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Published in final edited form as:
Hum Brain Mapp. 2009 November ; 30(11): 3812–3825. doi:10.1002/hbm.20809.

Thalamo-Frontal White Matter Alterations in Chronic Schizophrenia: A Quantitative Diffusion Tractography Study

Jungsu S. Oh, PhD[1,2], **Marek Kubicki, MD, PhD**[1,3], **Gudrun Rosenberger, MD**[1,4], **Sylvain Bouix, PhD**[1], **James Levitt, MD**[1,3], **Robert W. McCarley, MD**[3], **Carl-Fredrik Westin, PhD**[5], and **Martha E. Shenton, PhD**[1,2,6,*]

[1]Department of Psychiatry, Psychiatry Neuroimaging Laboratory, Brigham and Women's Hospital, Harvard Medical School, Boston, MA 02215, United States

[2]Brain Korea21 Division of Human Life Science, Seoul National University, Seoul 110-744, South Korea

[3]Clinical Neuroscience Division, Laboratory of Neuroscience, VA Boston Healthcare System, Brockton, MA, United States

[4]Department of General Psychiatry, Medical University Innsbruck, Innsbruck, Austria

[5]Laboratory Mathematical Imaging, Department of Radiology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA 02215, United States

[6]Surgical Planning Laboratory, MRI Division, Department of Radiology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA 02215, United States.

Abstract

Diffusion tensor imaging (DTI) and fiber tractography are useful tools for reconstructing white matter tracts (WMT) in the brain. Previous tractography studies have sought to segment reconstructed WMT into anatomical structures using several approaches, but quantification has been limited to extracting mean values of diffusion indices. Delineating WMT in schizophrenia is of particular interest because schizophrenia has been hypothesized to be a disorder of disrupted connectivity, especially between frontal and temporal regions of the brain. In this study, we aim to differentiate diffusion properties of thalamo-frontal pathways in schizophrenia from normal controls. We present a quantitative group comparison method, which combines the strengths of both tractography-based and voxel-based studies. Our algorithm extracts white matter pathways using whole brain tractography. Functionally relevant bundles are selected and parsed from the resulting set of tracts, using an internal capsule (IC) region of interest (ROI) as "source", and different Brodmann area (BA) ROIs as "targets". The resulting bundles are then longitudinally parameterized so that diffusion properties can be measured and compared along the WMT. Using this processing pipeline, we were able to find altered diffusion properties in male patients with chronic schizophrenia in terms of fractional anisotropy (FA) decreases and mean diffusivity (MD) increases in precise and functionally relevant locations. These findings suggest that our method can enhance the regional and functional specificity of DTI group studies, thus improving our understanding of brain function.

[*]Corresponding Author: Martha E. Shenton, Ph.D., Address: 1249 Boylston Street, Psychiatry Neuroimaging Laboratory, Boston, MA 02215, Tel: +1-617-525-1700 ; Fax: +1-617-525-6150; Email: shenton@bwh.harvard.edu.

Keywords

diffusion tensor imaging (DTI); Brodmann area (BA); internal capsule (IC); parametrization; chronic schizophrenia

Introduction

Diffusion tensor imaging (DTI) and fiber tractography have proven to be useful for investigating *in vivo* anatomical connectivity of white matter fiber tracts in the brain. However, while great progress has been made in terms of tract visualization, the quantitative analysis of output from fiber tractography remains difficult. An attempt to address this issue has been made with recently developed quantitative methods, such as tract-based spatial statistics (TBSS - Smith et al., 2006) and tract parametrization (Gong et al., 2005; Lin et al., 2006; Oh et al., 2007; Reich et al., 2007). Using these methods, quantitative measures of white matter integrity (e.g., fractional anisotropy (FA) and/or mean diffusivity (MD)) can be followed along the white matter fibers, and compared between groups.

As a number of investigators have speculated that schizophrenia is a disorder involving disconnectivity between distant brain regions (e.g., Weinberger et al., 1994; Kubicki et al., 2005), DTI has become the method of choice for quantifying white matter fiber tracts (see review in Kubicki et al., 2007). Early findings have shown reductions in integrity of whole white matter (Buchsbaum et al., 1998) as well as FA reduction in fronto-temporal connections including the uncinate fasciculus (Kubicki et al., 2002a, b), cingulum bundle (Kubicki et al., 2003; Wang et al., 2004), and arcuate fasciculus (Hubl et al., 2004). Loss of integrity has also been reported in the corpus callosum, particularly in the genu and splenium portions of this fiber tract (Foong et al., 2000; Agartz et al., 2001).

Another focus of attention has been thalamic frontal white matter projections, traveling through the internal capsule (IC) (Buchsbaum et al., 1998, 2006). The IC, in particular the anterior limb of the IC (AL-IC), is an important pathway involved in affect, attention, working memory, language and association brain functions, often reported to be abnormal in schizophrenia (Park et al., 2004;Buchsbaum et al., 2006;Zou et al., 2008). Also, and as noted by Nolte (2002), the thalamo-cortical projection through the AL-IC is the final pathway for all higher cognitive feedback loops, forming the thalamo-subcortical connections. Thus, structural abnormalities of fiber integrity (FA) or tissue microstructures (MD) in these fiber tracts could lead to functional disconnections of these networks, which, in turn, may underlie many of the behavioral and cognitive abnormalities observed in schizophrenia (Kubicki et al., 2005). In the study presented here, we further investigate FA and MD values in frontal projections of the mostly thalamic connections traveling through the AL-IC in schizophrenia.

Given that frontal projections of the IC include large bundles of fronto-subcortical fiber tracts that connect very distinct functional regions, we decided to use Brodmann areas (BA) as regions of interest (ROI) in order to divide IC projections into functionally-relevant parcellations. We thought that such an approach would provide more functional homogeneity compared with parcellation methods that are based on geometric divisions such as sulcal-gyral parcellation (e.g., Fischl et al., 1999; Park et al., 2008). In addition, we expected that this BA ROI approach would be useful for extracting fibers that are not only similar in function but also in appearance, thus improving parametrization. Furthermore, this approach is different from previous attempts to use cortical gray matter parcellation as a segmentation tool for reconstructing fiber tracts (Park et al., 2008; Thottakara et al., 2006), in that the focus is on parcellation of white matter structures in the brain.

With respect to fiber tractography, several issues need to be addressed. The most commonly-used tractography method consists of seeding fiber tracts in one region of the brain and employs a maximum likelihood orientation-based tracing technique to follow the path of the fibers. This deterministic method, however, is known to be very sensitive to noise and it lacks robustness, especially in constructing fiber tracts with crossing and fanning along their paths (Peled et al., 2006). Probabilistic tractography methods have been developed to try to resolve these issues (Behrens et al., 2003, 2007; Friman et al., 2003; Parker et al., 2003). Such methods are particularly good at addressing uncertainties in fiber bundle orientations, and at enabling researchers to use gray matter ROIs as seed points for fiber tractography. However, these methods usually involve tremendous computation in terms of estimation/sampling of random fiber orientations.

An alternative is to use deterministic tracing, and to seed the fibers in every location of the brain. This technique, called whole brain seeding-based tractography, generally has shown significantly better tracking results than regional seeding, as many more fibers are initiated (e.g., Conturo et al. 1999; Mori et al. 1999; Park et al., 2003; Huang et al., 2004). This tractography strategy also tends to be more efficient in terms of computation compared to probabilistic approaches. Many researchers thus employ whole brain tractography in order to construct group-based probabilistic maps of specific fiber tracts (e.g., Ciccarelli et al., 2003, 2005; Huang et al., 2005; Parker et al., 2005; Thottakara et al., 2006).

After tracing of fiber paths, information about their integrity needs to be computed so that it can be compared between groups. A common approach is to average values of FA and diffusivity for the entire fiber tracts. However, this method is not sensitive to local changes of the diffusion properties along the tracts. Thus more recently, methods of tract parametrization have been introduced in order to measure, and to compare, diffusion properties within subjects, and between populations (e.g., Gong et al., 2005; Lin et al., 2006; Reich et al, 2007; Oh et al., 2007). For example, Gong et al. (2005) established a cingulum bundle (CB)-specific “angular coordinate” system for tract parametrization. Others have focused on arc-length or normalized arc-length to subdivide (or parameterize) fiber tracts (e.g., Lin et al., 2006; Reich et al, 2007; Oh et al., 2007). The arc-length-based coordinate system is based on a transformation that converts rectangular Cartesian coordinate systems to a normalized coordinate system along the fiber bundle. These methods are similar to each other, in that they divide the fiber tracts into several segments, in order to provide better regional specificity than conventional methods (e.g., bulky ROI-based analysis). In particular, our previous study (Oh et al., 2007) demonstrated the usefulness of three-dimensional (3-D) parametrization of the corpus callosum (CC), in terms of more regional specificity. In this previous study, we successfully differentiated group-associated fiber integrity differences in the CC, the largest bundle of white matter tracts in human brain. As our objective was to have a quantitative DTI analysis based on a reliable fiber tract extraction with functional specificity, and also further parametrization with regional specificity, we decided to combine the BA ROI parcellation approach with the longitudinal tract parametrization.

Finally, we used a statistical analysis in order to investigate group-associated differences of DTI measures (i.e., FA values, measures believed to be estimators of fiber tract coherence/integrity, and MD values, measures of disruption of tissue microstructures) along the entire length of each fiber tract. Thus using whole brain tractography, BA-based ROI, and tract parametrization methods, we conducted a quantitative DTI analysis for differentiating male chronic schizophrenia patients from male normal controls, in terms of fronto-subcortical white matter alterations.

Materials and Methods

Participants

Eighteen male patients with chronic schizophrenia were recruited from inpatient, outpatient, day treatment, or foster care programs at the Veteran's Administration (VA) Boston Healthcare System, Brockton, Massachusetts, and 21 male normal controls were recruited through newspaper advertisements. Inclusion and exclusion criteria consisted of: aged 18–55, IQ > 75, no history of seizures or head trauma with loss of consciousness or a neurological disorder, and free from alcohol/drug dependences in the past 5 years. A trained interviewer diagnosed patients on the basis of the DSM-IV criteria using the SCID-P (Spitzer et al., 1990a) in conjunction with information obtained from medical records. Using the SCID-NP (Spitzer et al., 1990b) and SCID-II (Spitzer et al., 1990c), normal controls were excluded if they had a history of Axis I mental disorders (in themselves or their first-degree relatives), or an Axis II disorder. All patients were receiving antipsychotic medication at the time of testing. In addition to the IQ, the premorbid intellectual abilities were evaluated using the WAIS-III measure of IQ as well as the scaled reading score of the Wide Range Achievements Test 3 (WRAT3-RS), the latter considered an appropriate measure of premorbid IQ in patients with schizophrenia, since IQ measured by the WAIS-III may be compromised by illness. Socioeconomic status (SES) of schizophrenia and normal controls, and those of their parents (PSES), was evaluated using the Hollingshead two-factor index (1965). Clinical symptoms were measured using the Scale for the Assessment of Negative Symptoms and the Scale for the Assessment of Positive Symptoms (SANS/SAPS - Andreasen, 1981, 1984). The study was approved by the local IRB committees at Brigham and Women's Hospital and the VA Boston Healthcare System, and all study participants gave written informed consent prior to study participation. A subset of subjects used in this investigation was also used previously in other DTI investigations (Rosenberger et al., 2008; Kuroki et al., 2006; Kubicki et al., 2005).

MR image acquisition

Line Scan Diffusion Imaging (LSDI) was used to acquire DTI images (Gudbjartsson et al., 1996; Maier et al., 1998) using a quadrate head coil on a 1.5T GE Echospeed system (General Electric Medical Systems, Milwaukee, Wisconsin) at the Brigham and Women's Hospital, Harvard Medical School, Boston, MA. For each line, six DWIs were acquired with diffusion gradients ($b = 1000$ sec/mm^2) along six non-collinear directions and two images were acquired with minimal diffusion gradient ($b = 5$ sec/mm^2). Other imaging parameters included: field of view (FOV) 220×165 mm^2, scan matrix 128×96, and image matrix 256×192. Four millimeter coronal oblique slices were acquired, and these were aligned to the AC-PC line and interhemispheric fissure, with 1 mm gap between slices. To compensate for a relatively coarse interslice resolution, cubic spline interpolation was conducted along the slice direction in order to make the DTI volume isotropic ($0.86 \times 0.86 \times 0.86$ mm^3).

To define the white matter segmentation masks with anatomical precision, a series of 124 contiguous coronal images were acquired using a spoiled gradient recalled acquisition (SPGR) MR sequence with the following parameters: TR = 35 ms, TE = 5 ms, flip angle 45º, FOV 240×240 mm^2, number of excitations (NEX) = 1.0, matrix = 256×256, axial slice thickness 1.5mm, resulting in voxel dimensions of $0.94 \times 0.94 \times 1.5$ mm^3.

ROI definition and preprocessing

In order to extract fiber tracts of interest (i.e., frontal projections from the IC), we used a whole brain seeding tractography technique, followed by a selection process that only preserves tracts going through specific combinations of regions of interest (ROIs) (Conturo et al., 1999; Mori et al., 1999; Park et al., 2003; Huang et al., 2004). Indeed, the fibers in the

anterior limb of the internal capsule do not exclusively connect frontal lobe and thalamus. However, according to previous internal capsule population map by Zarei et al. (2007), most of them are thalamo-frontal connections. Internal capsule ROIs were drawn on the FA (fractional anisotropy) maps. A single rater (G.R.), blind to diagnosis, gender and age, drew ROIs for the entire internal capsule (anterior and posterior limb, as well as genu). The borders were placed generously, including tissue surrounding the internal capsule in order to include all fibers passing through the capsule. This was possible, since Brodmann area (BA) ROIs were selected to eventually exclude extraneous fibers. From the resulting bulky fiber bundle, the fibers connecting the internal capsule and the frontal lobe were extracted. After the ROIs were drawn, they were up-sampled, along with the entire FA map, into isotropic 0.86 mm cubic volumes using trilinear interpolation, and then the ROI boundary surface, modeled by a 3D triangular mesh, was extracted using the *marching cubes* algorithm (Lorensen and Cline, 1987). The resulting surface was regularized by a mesh-based smoothing, a method for decreasing distances between points on the mesh and their neighboring points.

Next, the second set of ROIs within the frontal lobe was selected using a BA atlas (BA 9, 10, 11, 32, 44, 45, 46 and 47 were selected), which is part of MRIcro software version 1.4 (http://www.sph.sc.edu/comd/rorden/mricro.html). Since the atlas is defined in common "template" space, it needs to be transformed (registered) to each subject's space. For the best coregistration results, for each subject separately, we used first a nonlinear registration to the individual anatomical T1 SPGR image, followed by an affine registration to the DTI image. This process was done using SPM2 (http://www.fil.ion.ucl.ac.uk/spm/software/spm2/). In addition, as emphasized by Thottakara et al. (2006), in order to keep the ROIs intact during spatial transformation, nearest neighbor interpolation was employed in all spatial transformation steps. Since this template was constructed from a number of subjects, we observed that the boundary of BAs was mildly over-inclusive, i.e., these ROIs included also white matter regions instead of just gray matter regions. Therefore, we excluded white matter regions from the BA ROIs by using a smoothed (Gaussian kernel with four millimeter full-width-at-half-maximum [FWHM]) FA-based mask. Using this mask, we could exclude the high FA-value regions (FA > 0.3), generating final cortical BA ROIs.

Taken together, all of these steps resulted in the generation of two separate sets of ROIs: (1) the internal capsule (IC) white matter ROIs, and (2) cortical BA ROIs, which were used later for the fiber tract extraction (see Fig. 1B).

Diffusion tensor tractography and postprocessing

Diffusion tensor estimation and fiber tractography were conducted using in-house fiber tracking software (Oh et al., 2007). As mentioned in the previous section, we used a whole brain seeding strategy followed by a multiple-ROI selection technique. Our experience (Oh et al., 2007), and the experience of others, suggest that it is a robust way of tracing fiber paths in DTI in the presence of noise and fiber crossings (e.g., Conturo et al., 1999; Mori et al., 1999; Park et al., 2003; Huang et al., 2004).

We used an FA threshold of 0.1 for both the seeding and stopping criterion for the fiber tracing. After all of the brain fiber tracts were reconstructed, we applied a multiple ROI selection method to segment parts of the IC that project to each individual BA. Next, in order to minimize parametrization errors due to the fiber length and fiber shape variability within the gray matter, all surviving fiber tracts were cut using the boundaries of the two anatomical landmarks (i.e., white matter IC ROI and gray matter BA ROIs), and subjected to tract parametrization along the direction of principal diffusion (tract-length parametrization- Lin et al., 2006; Oh et al., 2007; Reich et al., 2007) (Fig. 1C). Specifically, each tract in each subject was divided into percentiles (i.e., 100 segments of equal length,

starting from the IC ROI forward), thus providing further correspondence between specific locations along the tracts and subjects.

To compare intrasubject variability versus intersubject variability along tracts, we calculated two sets of variance, i.e., intra-subject (across-location) variances and inter-subject (across-subject) variances. More specifically, let's assume that we have a parameterized tractography of i^{th} subject, $X_i(s) = [x_i(s), y_i(s), z_i(s)]$ (s = 1, 2, …, 100; where s denotes each location in the 100 bins-parameterized tract) and corresponding FA (or MD) values, $F_i(s) = F_i(x_i(s), y_i(s), z_i(s))$.

Then, regarding intra-subject variability, we have mean and variance of FA (or MD) values for each subject:

$$\overline{F}_i = \sum_{s=1}^{100} F_i(s)/100$$
$$\mathrm{var}(F_i) = \sum_{s=1}^{100} [F_i(s) - \overline{F}_i]^2/100\text{: ``intra-subject variance''} \quad (1)$$

Regarding inter-subject variability, we have mean and variance of FA (or MD) values for each location:

$$\overline{F}(s) = \sum_{i=1}^{Ns} F_i(s)/\mathrm{Ns}\ \text{(Ns:number of subjects)}$$
$$\mathrm{var}(F(s)) = \sum_{i=1}^{Ns} [F_i(s) - \overline{F}(s)]^2/\mathrm{Ns}\text{: ``inter-subject variance''} \quad (2)$$

We tested whether or not intra-subject variances are different from inter-subject variances using Wilcoxon Rank-Sum Test, also known as the Mann-Whitney U-Test.

Statistical analysis

T-student tests were conducted to assess group differences in age, SES, PSES, education and intelligence quotient (IQ). As for the diffusion measures, since correspondences between specific locations along the tracts and subjects were well established by the aforementioned methods, statistical analyses of group differences in corresponding fiber tracts were relatively straightforward. We conducted a statistical analysis as follows. First, we employed three-way analysis of variance (ANOVA), in order to determine group, region, or side interactions for FA values. Second, we used multiple one-way ANOVAs, in order to determine which tract contributed to those effects. Finally, we conducted *post hoc* protected independent t-tests along the "parameterized" tracts for each subject, in order to determine region-specific group differences. The same methods were applied to Mean Diffusivity (MD) values.

In addition, we further analyzed the data using age and MODE (Ennis and Kindlmann, 2006) as possible confounds. Considering the age range of our subjects (Normal control: 42.7±6.6, Schizophrenia: 39±8.7), we included age in our analyses as a possible confound for FA analysis. In addition, we used a new DTI measure termed MODE developed by Ennis and Kindlmann (2006), where negative MODE is an indirect measure of fiber crossing. Since fiber crossing might result in underestimated FA values, we introduced MODE as an additional regressor before conducting t-tests of FA values. In fact, MODE and

FA are theoretically orthogonal shape measures, and together with tensor norm they form a shape basis that can describe the shape of any diffusion tensor, so if there is any correlation between them, this is induced by the data. In an effort to introduce MODE as a possible fiber crossing confound of FA, however, we used a second order regression (See following formula).

$$FA = a_0 + a_1 MODE + a_2 MODE^2 + \varepsilon$$

a_0, a_1, a_2:regression coefficients, ε:residual

In addition, false discovery rate (FDR) was applied to the first level statistical analysis for the purpose of multiple-comparison correction.

Results

Although there were significant group differences in education, WAIS-III IQ and SES ($p<0.001$ for all), there were no significant group differences in age, PSES, handedness or WRAT3-RS (see Table 1).

The results of three-way ANOVAs for DTI measures (FA/MD values) are summarized in Table 2. Both DTI measures demonstrated a significant main effect for group, as well as a main effect for region, but no side effect, or group by region interaction.

The multiple one-way ANOVAs that followed revealed significant group effects for FA/MD values of IC projections to each frontal BA (also listed in Table 3). For the convenience of interpretation of functionally similar Brodmann regions, we describe the significant results of BA 9/46 together and BA 44/45 together in all the following descriptions:

Simultaneous decrease in FA and increase in MD were observed only for the dorsolateral prefrontal projections (DLPFC - BA 9/46) ($F = 4.7$, $p = 0.03$ for the FA), and ($F = 14$, $p < 0.001$ for the MD). Decreased FA without changes in MD was observed for the anterior cingulate projections (ACC - BA 32) ($F = 6.31$, $p = 0.01$) and BA 44/45 projections (that include Broca area on the left) ($F = 5.86$, $p = 0.02$). Finally, increased MD without FA changes was observed for the frontal pole projections (FP - BA 10) ($F = 6.36$, $p = 0.01$), the orbitofrontal projections (OFC - BA 11) ($F = 9.52$, $p < 0.01$) and the inferior-prefrontal projections (IPFC – BA 47) ($F = 5.49$, $p = 0.02$).

Finally, *post hoc* independent t-tests revealed regionally specific group differences for both DTI measures (FA and MD), localized as follows: FA showed decreases in the proximal (thalamic) part of the BA 9/46 projections, and in the middle part of the BA 9/46 and the BA 44 projections, while MD showed increases in the proximal and distal (cortical) parts of the BA 9/46, BA 47, BA 10 and BA 11 projections (See also Figure 2–3 for more details). According to our results, not all ROI connections were affected in the same way (see Figure 2 and Figure 3). More specifically, unlike FA differences (which were detected in DLPFC and BA 44/45) in proximal (near internal capsule) and middle parts, most MD differences were found in the distant (closer to the cortex) parts of the fiber projections to the rostral BA.

Figure 4 demonstrates results of FA analysis before and after removing possible confounds of age and mode from the analysis, demonstrating that neither fiber crossing nor age significantly affected the results.

We found that for most regions intersubject variability (subject vs. subject variability of mean FA value at each location) was equal or smaller than intrasubject variability (location

vs. location variability of regional FA values in each subject), with the exception of area BA 47, where the intersubject variability was greater than intrasubject variability (See Table 4 for detail).

Discussion

Results of our study demonstrate local decrease of FA and/or increase of MD values, in patients compared with controls, within several functionally specific fronto-thalamic tracts, including the projections to and from DLPFC, ACC, BA 44/45, frontal pole, orbitofrontal cortex and inferior prefrontal cortex. These findings were independent of IQ, parental socioeconomic status, and age. To the best of our knowledge, the present study is the first to combine a BA-specific ROI selection and a tract parametrization technique. It is also the first study that applies this technique to thalamo-frontal white matter connections in schizophrenia. Of further note, our results indicate disrupted fiber integrity (FA decreases) and disrupted tissue microstructures (MD increases) in schizophrenia that concur with results of previous histopathologic studies where abnormalities in oligodendrocyte function have been reported (Uranova et al., 2001, 2004).

Previous studies investigating these connections have used more generic approaches. For example, some studies have focused on the integrity and asymmetry of the AL-IC, using a voxel-based morphometry (VBM) approach, and reported decreased FA, altered magnetization transfer (MT) and diminished asymmetry within this region (Park et al., 2004; Kubicki et al., 2005). Others have used fiber tractography, measuring the length of fronto-thalamic fiber tracts and reporting their shortening in schizophrenia (Buchsbaum et al., 2006). Finally, Kim et al. (2008) used sulcal/gyral parcellation to separate and measure anatomically specific thalamo-cortical projections, and reported increased mean MD in thalamo-orbitofrontal and thalamo-parietal-occipital-temporal fiber tracts in patients with schizophrenia.

As opposed to other tractography approaches, our investigation attempted to separate fronto-thalamic tracts based on functional, rather than anatomical cortical segmentation. The advantage of this method is that extracted fiber tracts carry information to and from functionally homogenous regions of gray matter, and their integrity is inevitably related to particular brain function of specific BA that was used for tract segmentation. In this way, the relationship between anatomy and function, and their associated abnormalities in schizophrenia, are likely easier to establish. In addition, we included tract parametrization, which allows us to perform group comparison at any given position along the extracted fiber bundles, thus further increasing sensitivity and specificity. Our approach essentially combines the strengths of two different conventional methods: 1) In the VBM approach, group comparison of white matter integrity can be studied for every voxel of the human brain, but differences cannot be straight-forwardly assigned to specific fiber bundle (Park et al., 2004; Kubicki et al., 2005). Using inverse normalization of significant difference regions, however, one can conduct post-hoc tractography to assign fiber tracts to regional differences. Nonetheless, this approach will require additional efforts to warrant intersubject homology of each voxel in each subject. Alternatively, we tried to define intersubject homologous points using a tract-oriented method called tract parametrization. More importantly, our method is less affected by inter-subject registration of white matter features and its errors. 2) In the tractography approach, specific tracts are extracted, but group comparison is being carried on the diffusion properties averaged over the entire tract, rather than studied for each voxel of the tract separately (and thus the possible local, subtle differences might be washed out by the averaging) (Rosenberger et al., 2008; Kim et al., 2008).

Region-by-region descriptions with respect to FA and/or MD differences are as follows: 1) The DLPFC related part of the AL-IC, that is the tract carrying connections mostly between DLPFC and medial-dorsal thalamic nucleus (MDN), demonstrated both decreased FA and increased MD values. This bundle, by virtue of its anatomical connections, likely plays an important role in affect, association and working memory functions, all reported to be abnormal in schizophrenia (Bunney and Bunney, 2000; Cannon et al., 2005; Schlosser et al., 2007). 2) Decreased fiber integrity in thalamic projection to BA 44/45, which includes Broca's area, suggests a disruption in the language network (Felleman and Van Essen, 1991; Petrides and Pandya, 1988) that might elucidate language process abnormalities in schizophrenia (Burns et al., 2003; Hubl et al., 2004). The ACC, thalamic projection to which showed decreased FA values as well, is related to cognitive functions including executive attention, reward anticipation, decision-making and affective functions, which are also abnormal in schizophrenia (Quintana et al., 2004; Szeszko et al., 2007). 3) Although not frequently addressed in previous studies, increased MD values in IC projections to orbitofrontal cortex and inferior prefrontal cortex are likely important as they underlie cognitive processes, including decision-making in orbitofrontal cortex (Hutton et al., 2002), and syntax processing in spoken and signed languages in inferior prefrontal cortex (Kubicki et al., 2003), all reported to be abnormal in schizophrenia.

According to our results above, not all ROI connections were affected in the same way (see Figure 2 and Figure 3). Since we found significant FA (but not MD) changes in IC connections to area 9, and MD (but not FA) changes in IC projections to area 46, DLPFC connectivity results should be treated with caution. One possible source of such a differential pattern of changes in schizophrenia might be due to an anatomical difference in the way that the thalamocortical tracts are affected for these two ROIs in schizophrenia, as well as individual variability of Brodmann areas 9 and 46, which was demonstrated previously by Rajkowska and Goldman-Rakic (1995). Since the intersubject variability for most regions was equal or smaller than intrasubject (regional) variability, we believe it is appropriate to perform not only "bulky" tract analysis (i.e., ANOVAs) but also "regional" tract analysis (i.e., parameterization). However, since BA 47 showed greater intersubject variability of MD values, this region should be treated with more caution.

Interestingly, MD differences were seen along the tracts when reaching the cortex, and all correspond with rostral BAs. Indeed, we have utilized line scan diffusion imaging (LSDI) for DTI acquisition. Since this imaging technique is relatively free from image distortions observed with EPI-based DTIs, we think the results are not an artifact. Instead, we think that the nature of this dissociation could be due to the fact that the mean diffusivity (MD) measures, which basically reflect tissue micro structure disruption, could be more influenced by architectural, neuro-developmental, and more importantly, cortical reorganization than FA, and that MD might be more sensitive to changes in low coherence regions, and FA in more coherent regions.

The following limitations should be noted when interpreting our results. As noted by Smith et al. (2006), our parametrization method, similar to all parametrization-based approaches tends to be more reliable for large fiber tracts but less so for smaller bundles.

As mentioned above, our tracts of interest (frontal projection of the IC tracts) interconnect gray matter regions including frontal lobe and thalamus. To better construct these gray matter-relevant areas, we chose a relatively low FA threshold (0.1) for the seeding and stopping criteria of fiber tractography. Although low FA values, which also imply high fiber orientation uncertainties, can cause possible shape variability of the reconstructed white matter tracts, the parametrization has been regularized by cutting tracts between two ROIs (Figure 1).

Based on whole brain seeding, we were able to improve the robustness of the fiber tractography in the presence of uncertainty of the fiber orientation due to noise and fiber crossings. Whole brain tractography, however, is not an ultimate solution for these problems, and methods that explicitly model tract orientation uncertainty (such as stochastic approaches (Behrens et al., 2003; Parker et al., 2003; Friman et al., 2003)) need to be applied. Another consideration is to use high angular resolution diffusion imaging (HARDI), including Q-ball imaging (Tuch, 2004) as used by Schmahmann et al. (2007), although such an approach might be unrealistic in clinical studies due to the extremely long acquisition time.

As demonstrated by Rajkowska and Goldman-Rakic (1995), Amunts et al. (2007) and Malikovic et al. (2007), individual variability of Brodmann areas, not captured by a BA template approach, should be considered when interpreting the results. One study has also been conducted using gyral and sulcal borderlines for tract definition on the basis of cortical surface parametrization (Park et al., 2008). Since each approach has their pros and cons (more functional specificity for Brodmann ROIs vs. better anatomical precision for gyral ROIs), more experiments are needed in order to demonstrate the pros and cons of one method versus another. In addition, BA ROIs are easy-to-define using simple spatial transformation, which is the reason why voxel-based analyses are so popular in all neuroimaging studies.

Finally, we should note that the spatial resolution of our scans was relatively low, and thus partial volume effects might cause potential artifacts in data analysis and coregistration. We also note that the sample size of participants, although comparable with most DTI studies to date, was relatively small. In addition, we evaluated chronic schizophrenia only, medicated subjects only, and men only. Future studies need to evaluate patients with schizophrenia early in their illness long term neuroleptic use is minimal. Previous publications suggest that history of substance abuse, especially its duration (Pfefferbaum et al., 2008), as well as dependence could be a potential confounding factor for DTI results. We, however, excluded subjects with a history of substance dependence and we excluded subjects with substance abuse in the last year. We nonetheless did not have the data available to test more specifically for such a relationship, and future studies should include more detailed information regarding substance abuse and dependence in schizophrenia and its possible association with white matter pathology. Female patients should also be included to evaluate gender differences in this disorder. Similarly, due to using anisotropic voxels and relatively fewer number of diffusion gradient directions, we can expect the statistical results might be biased by partial volume effects that can not be radically resolved by image volume interpolation. In addition, there is an argument that interpolating potentially underestimates FA values, and that FA estimation errors depends on resolution, especially in regions of fiber crossings (Oouchi et al., 2007).

Conclusion

In summary, this study is the first schizophrenia study to combine a BA-specific ROI approach and tract parametrization to compare diffusion properties of the thalamo-frontal projections in schizophrenia compared with healthy controls. Based on our findings, we believe that our method improves regional and functional specificity of the spatial statistics of the diffusion properties, forming a potential promising tool for detecting pathological processes in important white matter tracts in schizophrenia.

Acknowledgments

We gratefully acknowledge support from the Korea Research Foundation Grant funded by the Korean Government (MOEHRD) (KRF-2006-352-D00220 to JSO), from the second stage Brain Korea 21 Project in 2008, Division of Human Life Science to (JSO), from the National Institute of Health (K05 MH070047 and R01 MH 50747 to MES), from the Department of Veterans Affairs Merit Awards (to MES, RWM), CIDAR (1 P50 MH080272-01 to MES, RWM), and from the VA Schizophrenia Center Grant (to MES, RWM). This work is also part of the National Alliance for Medical Image Computing (NAMIC), funded by the National Institutes of Health through the NIH Roadmap for Medical Research, Grant U54 EB005149 (to MES, MK).

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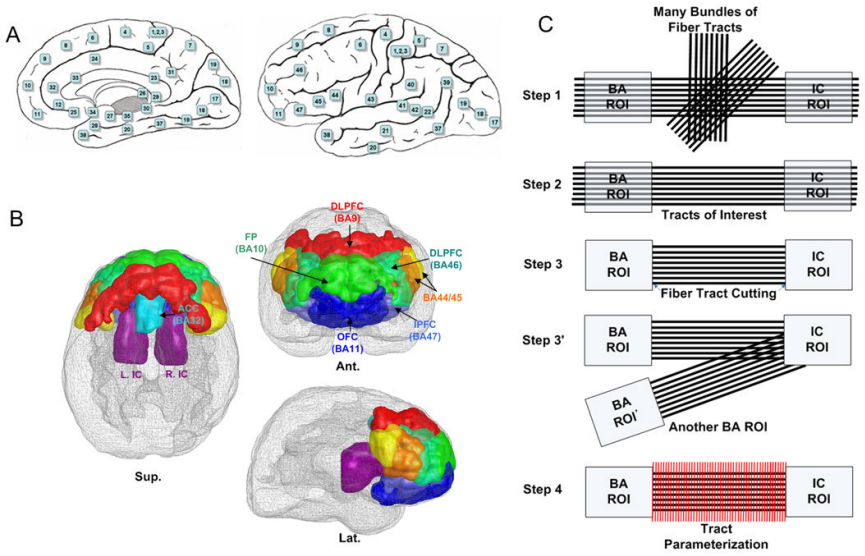

Fig. 1. BA and IC ROIs selection and tract parametrization

Footnote: Figure A (adapted from http://en.wikipedia.org/wiki/Brodmann_area), represents atlas of BA ROIs displayed on both lateral and medial surfaces of the brain. Figure B illustrates frontal ROIs in conjunction with IC ROI in one random case, and represents a schematic of overall flow of tractographic data processing (C) (see details in text). Abbreviations: ROI: region of interest; IC: internal capsule; BA: Brodmann area; Ant.: anterior view; Sup.: superior view; Lat: lateral view; DLPFC: dorsolateral prefrontal cortex; FP: frontal pole; OFC: orbitofrontal cortex; IPFC: inferior prefrontal cortex; ACC: anterior cingulate cortex

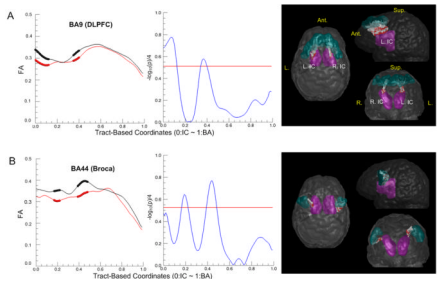

Fig. 2. Results of tract parametrization and FA group comparison

Footnote: FA distributions along the tracts, and group differences for tracts interconnecting IC and three Brodmann areas (BAs). In the left column, thicker lines represent group differences at $\alpha<0.05$ corrected using false discovery rate (FDR)). Middle column illustrates logarithmically scaled P values, with the red line representing significance cut-off. Right-hand column shows ROIs used (IC- dark pink, BAs-dark cyan). In addition, we present an illustrative visualization using image and tractographic data from a normal control subject. The colors indicate no differences (white) and significant differences, i.e., FDR-corrected $\alpha < 0.05$ (red).

Abbreviations: BA: Brodmann area; IC: internal capsule; FA: fractional anisotropy; DLPFC: dorsolateral prefrontal cortex; Ant.: anterior; Sup.: superior; L.: left; R.: right;

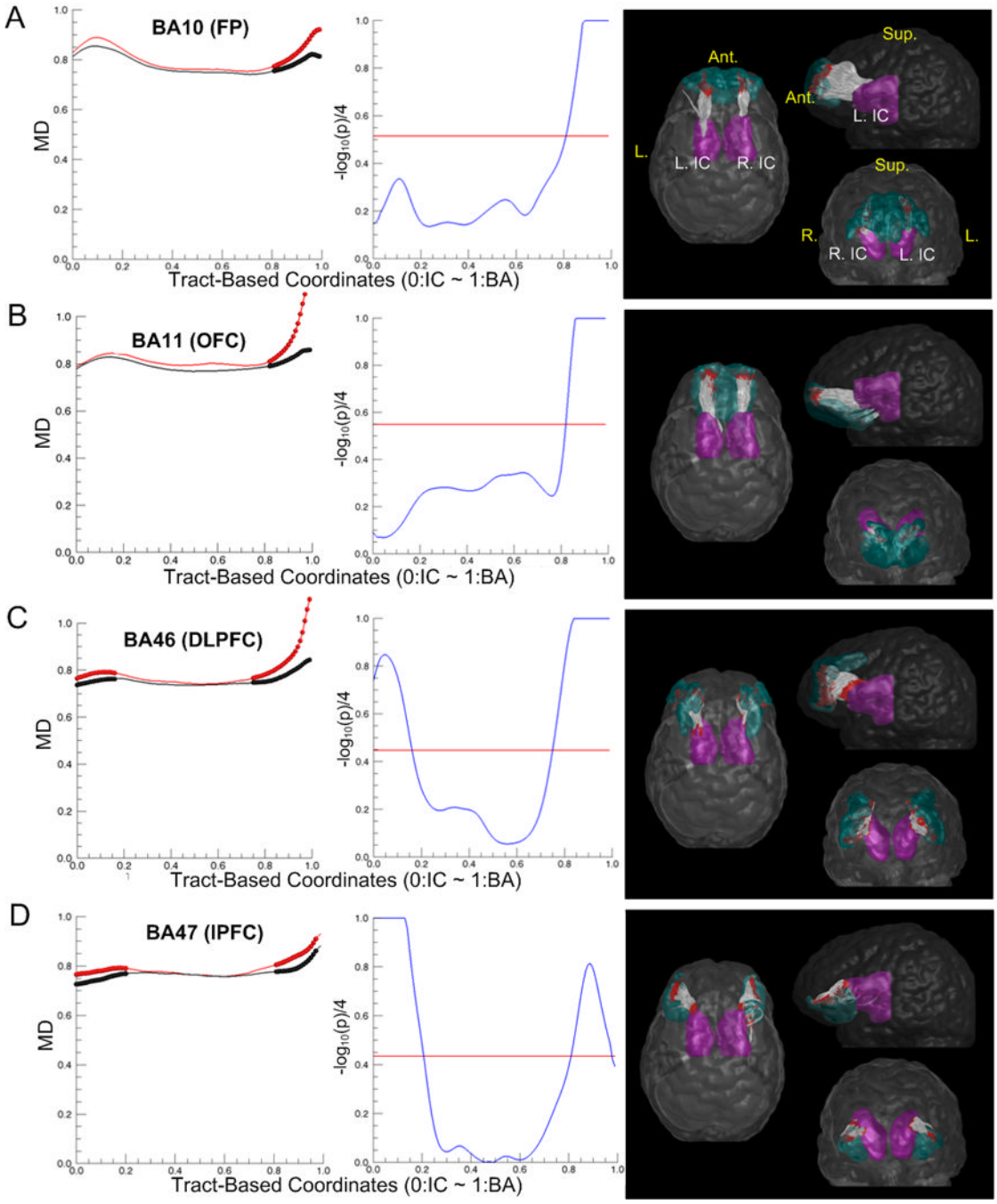

Fig. 3. Results of tract parametrization and MD group comparison

Abbreviations: BA: Brodmann area; IC: internal capsule; MD: mean diffusivity; DLPFC: dorsolateral prefrontal cortex; FP: frontal pole; OFC: orbitofrontal cortex; IPFC: inferior prefrontal cortex; Ant.: anterior; Sup.: superior; L.: left; R.: right;

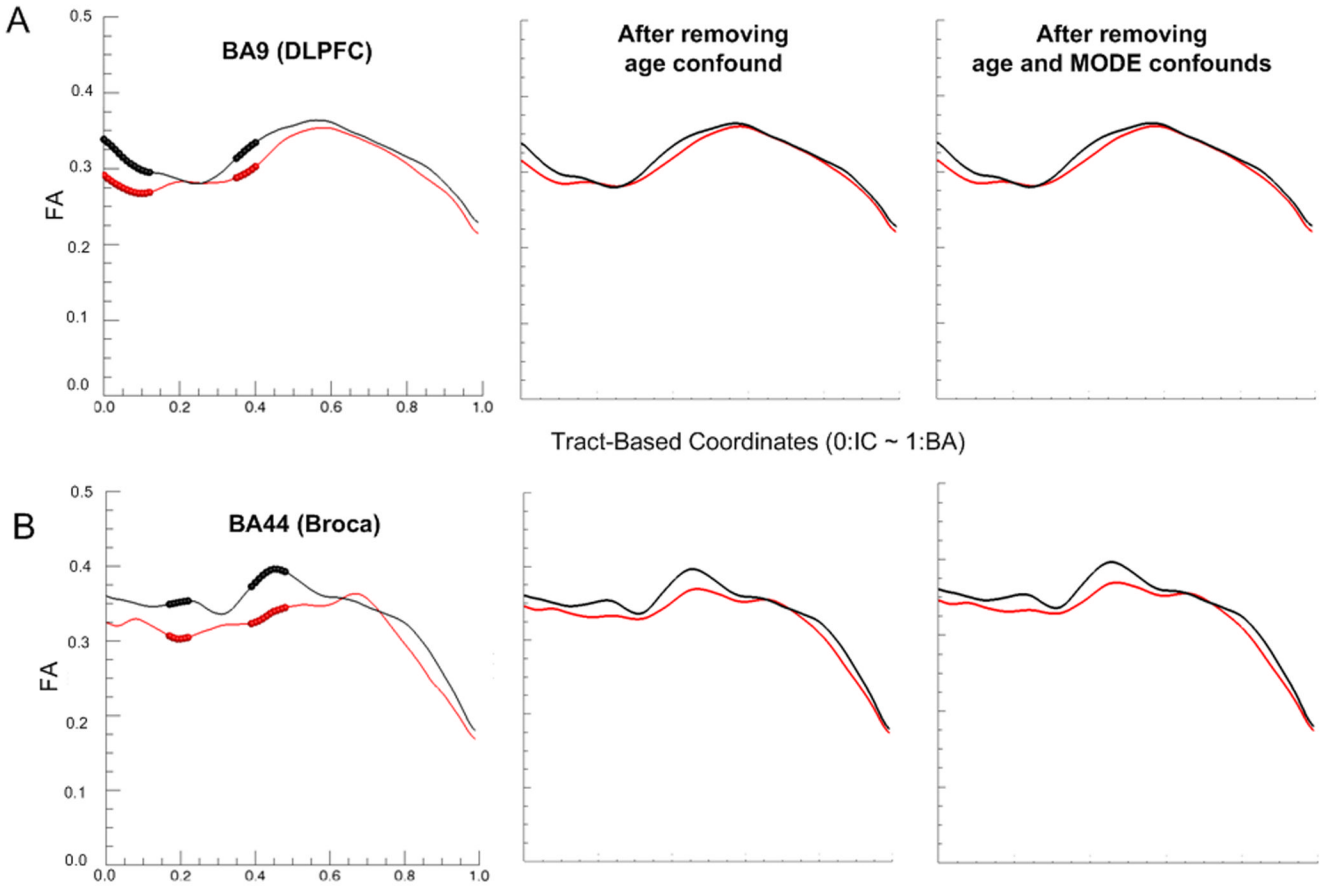

Fig. 4. Controlling for possible confounds of age and fiber crossing (MODE)

Abbreviations: FA: fractional anisotropy; DLPFC: dorsolateral prefrontal cortex;

Table 1

Demographic characteristics for SZs and NCs

Footnote: Demographic attributes that did not show significant group differences in bold. In addition, significant p values also in bold.
Abbreviations: SZs: chronic schizophrenia subjects; NCs: normal controls; IQ: intelligence quotient; WRAT3-RS: wide range achievements test 3 reading scaled; LH: left hand; RH: right hand

			T-Student Test (two-tailed)		
Characteristics	**SZs (n = 18)**	**NCs (n = 21)**	**t**	**df**	**P**
Age (years)	39 ± 8.7	42.7 ± 6.6	1.3	38	0.21
Education (years)[a]	12.4 ± 2.0	15.6 ± 2.4	4.1	37	**<0.001**
WAIS-iii IQ[b]	93.3 ± 13.6	108.7 ± 12.6	5.0	33	**<0.001**
WRAT3 RS[c]	105.0 ± 10.7	103.4 ± 11.8	−0.34	24	0.73
SES[a,d]	3.8 ± 1.2	2.2 ± 1.0	−6.5	37	**<0.001**
Parental SES[a,d]	2.9 ± 1.0	2.5 ± 1.2	−0.95	37	0.35
LH Finger tapping[e,f]	39.8 ± 9.2	44.4 ± 7.0	1.7	31	0.10
RH Finger tapping[e,f]	41.7 ± 8.2	48.3 ± 7.9	1.7	31	0.11

[a] based on 18 SZs and 20 NCs;

[b] based on 17 SZs and 17 NCs;

[c] based on 11 SZs and 14 NCs;

[d] Socioeconomic Status (with lower numbers representing higher SES);

[e] taps per 10 second period;

[f] based on 19 SZs and 13 NCs;

Table 2

Three-way ANOVA of DTI measures

Footnote: Group and region significant main effects on both FA and MD values. Significant results in bold.
Abbreviations: ANOVA: analysis of variance; FA: fractional anisotropy; MD: mean diffusivity; NC: normal control; SZ: chronic schizophrenia; LH: left hemisphere; RH: right hemisphere; BA: Brodmann area

Source	df	FA		MD	
		F	p	F	p
Main Effect of Group (SZ/NC)	1	17.9	**<0.001***	22.0	**<0.001***
Main Effect of Side (LH/RH)	1	2.6	0.11	0.39	0.53
Main Effect of Region (BAs)	7	10.9	**<0.001***	14.0	**<0.001***
Group × Region Interaction	7	1.7	0.11	0.31	0.95

Table 3

Multiple one-way ANOVAs of DTI measures for each BA

Footnote: Results of Fractional Anisotropy (FA) and Mean Diffusivity (MD) group comparison for the internal capsule projections to frontal Brodmann areas (BAs). Significant group differences in bold

Abbreviations: ANOVAs: analyses of variance; FA: fractional anisotropy; MD: mean diffusivity; BA: Brodmann area; DLPFC: dorsolateral prefrontal cortex; N/S: not significant

Region	df	FA				MD			
		mean		F	p	mean		F	p
		NC	SZ			NC	SZ		
BA 9[a]/46[b]	1	0.32±0.02	0.30±0.03	4.7	**0.03**	0.74±0.04	0.79±0.04	14	**<0.001**
BA 10[b]	1	N/S	N/S	N/S	N/S	0.78±0.04	0.81±0.03	6.3	**0.01**
BA 11[b]	1	N/S	N/S	N/S	N/S	0.80±0.03	0.84±0.05	9.5	**<0.01**
BA 32[a]	1	0.32±0.03	0.28±0.03	6.3	**0.01**	N/S	N/S	N/S	N/S
BA 44[a](/45)	1	0.34±0.03	0.31±0.05	5.9	**0.02**	N/S	N/S	N/S	N/S
BA 47[b]	1	N/S	N/S	N/S	N/S	0.77±0.03	0.79±0.03	5.5	**0.02**

[a] BAs with significant FA value differences;

[b] BAs with significant MD value differences;BA 9/46: DLPFC; BA 10: frontal pole; BA11: orbitofrontal cortex; BA32: anterior cingulate cortex; BA44/45: left hemispheric part of these areas includes Broca's area; BA 47: inferior prefrontal cortex

Table 4
Comparison between inter-subject and intra-subject variabilities of diffusion measures

		Mann-Whitney statistics	
BA	**P values**	**intra-subject variability**	**inter-subject variability**
9[a]	0.03*	1555	2345
44[a]	0.11	2206	1694
10[b]	0.05	1602	2298
11[b]	0.06	2277	1623
46[b]	0.35	2031	1869
47[b]	< 0.001*	2733	1167

[a] Comparison between intra-subject variability and inter-subject variability of FA values

[b] Comparison between intra-subject variability and inter-subject variability of MD values

* $P < 0.05$